09/917,292

WEST Search History

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L4	L3 and composition	5988	L4
L3	ribose	9312	L3
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☐ 1. Document ID: US 20020127285 A1

L5: Entry 1 of 6 File: PGPB Sep 12, 2002

DOCUMENT-IDENTIFIER: US 20020127285 A1
TITLE: Rhodiola and uses thereof

Abstract Paragraph (1):
The present invention relates to Rhodiola, preferably Rhodiola crenulata, to treat various conditions and diseases in mammals. Rhodiola crenulata is a Tibetan herb which has been discovered to have highly useful and beneficial properties heretofore unknown. Rhodiola crenulata is especially preferred to enhance blood oxygen levels, to enhance working capacity and endurance, to enhance memory and concentration, to enhance cardiac and cardiovascular function, to provide antioxidant effects, to protect against oxidation, to modulate testosterone and estradiol levels, to modulate sleep, and to enhance sexuability, such as improve sexual performance.

Summary of Invention Paragraph (2):
[0001] The present invention relates to compositions, articles of manufacture, extracts, compounds, methods of use, methods of treatment, methods of preparation, etc., which relate to plants of the genus Rhodiola, preferably Rhodiola crenulata, which have a variety of useful and beneficial effects, including, e.g., to enhance blood oxygen and nutrients levels, e.g., through enhancing oxygen transport, to enhance working capacity and endurance, to reduce muscle fatigue, to enhance memory and concentration, to reduce stress, to enhance cardiac and cardiovascular function, to provide antioxidant effects, to protect against oxidation, to provide anti-cancer effects, to promote DNA repair, to provide anti-radiation effects, to protect against radiation, to reduce inflammation, to increase insulin, to decrease levels of glucagon, to reduce histamine release, to reduce allergic reactions, preferably, to modulate testosterone levels, and to modulate sleep, especially to promote sleep, to modulate blood lipids, preferably, e.g., to lower cholesterol levels, to promote weight loss, and to enhance sexuability, such as improve sexual performance.

Summary of Invention Paragraph (4):
[0003] Rhodiola is a diverse genus of plants which includes more than 50 different species, including, e.g., algida, arctica, crenulata, elongata, gelida, imbricataishidae, iremelica, kirilowii, linearifolia, phariensis, pinnatifida, quadrifida, aff. quadrifida, rosea, sachalinensis, and wolongensis. These species vary from each other widely, differing in, e.g., chromosome number (e.g., Makoto et al., Journal of Japanese Botany, 70(6):334-338, 1995), chemical composition, morphology, medicinal properties, developmental stages (e.g., Ishmuratatova and Satsyperova, Rastitel'nye Resursy., 34(1):3-11, 1998), geographical distribution, etc. Scientific studies (e.g. Peng et al, Chinese Herb Medicine(1995), 26(4): 177-179, and Wang et al, Acta Phrmaceutica Sinica(1992), 27(2): 117-120) indicate constituents of Rhodiola crenulata include, e.g., salidroside, tyrosol, .beta.-sitosterol, gallic acid, pyrogallol, crenulatin, rhodionin, rhodiosin, among which, crenulatin, e.g., is found only in R. crenulata and has not been found in any other Rhodiola species. Rhodiosin and rhodionin exists in some, but not all, Rhodiola species.

Summary of Invention Paragraph (11):
[0010] Rhodiola can also be formulated with other active ingredients, such as

anti-oxidants, vitamins (A, C, ascorbic acid, B's, such as B1, thiamine, B6, pyridoxine, B complex, biotin, choline, nicotinic acid, pantothenic acid, B12, cyanocobalamin, and/or B2, D, D2, D3, calciferol, E, such as tocopherol, riboflavin, K, K1, K2). Preferred compounds, include, e.g creatine monohydrate, pyruvate, L-Camitine, .alpha.-lipoic acid, Phytin or Phytic acid, Co Enzyme Q10, NADH, NAD, D-ribose, amino acids such as L-Glutamine, Lysine, chrysin; pre-hormones such as 4-drostenedione, 5-androstenedione, 4(or 5-)androstenediol, 19-nor-4 (or 5-)-drostenedione, 19-nor-4 (or 5-)-androstenediol, Beta-ecdysterone, and 5-Methyl-7-Methoxy Isoflavone. Preferred active ingredients include, e.g., pine pollen, fructus lycii, hippophae rhamnoides, Salvia Miltiorrhiza, Ligusticum, Acanthopanax, Astragalus, Ephedra, codonopsis, polygola tenuifolia Willd, Lilium, Sparganium, ginseng, panax notogiseng, Garcinia, Guggle, Grape Seed Extract or powder, and/or Ginkgo Biloba.

Summary of Invention Paragraph (13):
[0012] Other active agents include, e.g., antioxidants, anti-carcinogens, anti-inflammatory agents, hormones and hormone antagonists, antibiotics (e.g., amoxicillin) and other bacterial agents, and other medically useful drugs such as those identified in, e.g., Remington's Pharmaceutical Sciences, Eighteenth Edition, Mack Publishing Company, 1990. A preferred composition of the present invention comprises, about 1%-100%, preferably about 20-70% Rhodiola crenulata extract, more preferably about 60%, said extract having about 0.5-10% salidroside content; 10-45% 5:1 extracted fructus lycii powder (5 kilograms of the herb is used to produce 1 kg of herb powder); 1-20% of hippophae rhamnoides powder; and, optionally, a pharmaceutically-acceptable excipient.

Summary of Invention Paragraph (14):
[0013] The present invention relates to methods of administering Rhodiola, especially Rhodiola crenulata, e.g., to enhance blood oxygen levels, to enhance working capacity and endurance, to reduce muscle fatigue, to enhance memory and concentration, to reduce stress, to enhance cardiac and cardiovascular function, to improve sexual ability, to provide antioxidant effects, to protect against oxidation, to provide anti-cancer effects, to promote DNA repair, to provide anti-radiation effects, to protect against radiation, to reduce inflammation, to increase insulin, to decrease levels of glucagon, to reduce histamine release, to reduce allergic reactions, preferably, to modulate testosterone levels, to increase male virality, to modulate sleep, especially to promote sleep. to modulate blood lipids, preferably, e.g., to lower cholesterol levels, to promote weight loss, to increase estradiol levels, etc., and other conditions and diseases as mentioned above and below.

Summary of Invention Paragraph (20):
[0019] Any effective amount of Rhodiola crenulata can be administered. In accordance with present invention, it has been demonstrated that intake of a standardized Rhodiola crenulata extract (e.g., having 0.1-110%. preferably 1-6%) salidroside by total weight of composition) produced a significant increase in total testosterone as compared to placebo. For example, after taking 2 grams of standardized rhodiola extract with 2% salidroside, once a day for a month, subjects showed about a 76% increase in total testosterone in the blood as compared to the 6.0% increase in total testosterone level after taking placebo for a month. These amounts, however, can be increased by any value, e.g., at least about 5%, 10%, 15%, 20%, 50%, 60% 70%, 75%, 100%, 2-fold, 5-fold, etc., over amounts which are present in the blood prior to administration.

Summary of Invention Paragraph (30):
[0029] Rhodiola can also be used to enhance or improved memory and concentration (such improved functions are to be distinguished from the more general brain stimulation which indicates increased non-selective neuronal activity, whereas the mentioned improved functions are selective, e.g., by stimulating specific parts of the brain or other organs, or by stimulating specific neural and hormonal systems); to reduce stress, e.g., lower blood pressure, reduce anxiety, promote calmness; to enhance cardiac and cardiovascular function (including, e.g., to protect against heart disease); to provide antioxidant effects and protect against oxidation; to provide anti-cancer effects, e.g., promote cessation of cell growth; to promote DNA repair; to provide anti-radiation effects and to protect against radiation, e.g., as

a sun-screen when applied topically to the skin; to reduce inflammation, e.g., systemic inflammation, skin inflammation (where Rhodiola can be administered topically), but with the proviso that it is not lung-inflammation, coughing, or bleeding associated with lung-inflammation and coughing, to increase insulin, to decrease levels of glucagon, to reduce histamine release, to reduce allergic reactions, to enhance sexual ability. Rhodiola crenulata in accordance with the present invention is preferably not used to treat external wounds, external burns, lung inflammation, and coughing.

Detail Description Paragraph (29):
[0057] A composition comprising effective amounts of Rhodiola crenulata can be administered to subjects to enhance levels of blood oxygen, to enhance working capacity and endurance, to enhance memory and concentration, to reduce stress, to enhance cardiac and cardiovascular function, to provide antioxidant effects, to modulate testosterone levels, to modulate sleep, and to improve sexual performance. to increase energy level, and to enhance memory and concentration. Such a composition can comprise, by weight:

CLAIMS:

15. A method of enhancing transport of blood oxygen, enhancing working capacity and endurance, or enhancing cardiac and cardiovascular function in a subject in need thereof, comprising, administering an effective amount of a Rhodiola crenulata to said subject, whereby said amount of Rhodiola is effective to reduce blood levels of lactate.

25. A method of claim 1, wherein said composition for increasing hormonal levels of testosterone or estradiol, comprising an effective amount of Rhodiola crenulata, and an effective amount of an herb selected from wild yam, Epimedium, Angelica, Lycium, panex ginseng, Ganoderma lucidum, Codonopsis, Eleutherococcus, fructus lycii, hippophae rhamnoides, Schisandra chinensis, Atractylodes, Yohimbe, Tribulus Terrestris, Guggle, Guarana, Cordyceps, Codonopsis, maca, or Ligustrum lucidum.

26. A method of claim 1, wherein said composition for increasing hormonal levels of testosterone or estradiol, comprising an effective amount of Rhodiola crenulata, and an effective amount 4-drostenedione, 5-androstenedione, 4(or 5-)androstenediol, 19nor-4 (or 5-)-drostenedione, 19-nor-4 (or 5-)-androstenediol, Beta-ecdysterone, and 5-Methyl-7-Methoxy Isoflavone.

27. A method of claim 12, wherein said composition for enhancing sleep, comprising an effective amount of Rhodiola crenulata, and an effective amount of an agent selected from Valerian, Melatonina, Kava Kava, St. John's Wort, Trytophan and 5-Hydroxytryptophan, Astragalus, Hops, Passionflower, Skullcap, Chamomile, He Shou Wu, Ashwaganda, fructus lycii, hippophae rhamnoides, or Lady's Slipper.

28. An herbal composition comprising: an amount of Rhodiola crenulata, and an amount of a herb selected from pine pollen, fructus lycii, hippophae rhamnoides, Salvia Miltiorrhiza, Ligusticum, Acanthopanax, Astragalus, Ephedra, codonopsis, polygola tenuifolia Willd, Lilium, Guggle, Kudzu, red clover, pine bark extract, St. John's Wort, Green tea, Yohimbe, Rehmania, Hawthorn, Guarana, Goldenseal, Fo-ti, Ephedra, Dong Quai, Cordyceps, Codonopsis, Citrus Aurantium, Sparganium, ginseng, panax notogiseng, Garcinia, Guggle, Grape Seed Extract or powder, Ginkgo Biloba., Creatine Monohydrate, D-Ribose, Pyruvate, NADH, Co-enzyme Q10, Camitine, or Conjuagated Linoleic Acid.

29. A composition of claim 28, comprising: 20-70% Rhodiola crenulata extract, said extract having 0.5-10% salidroside content, 10-45% 5:1 extracted fructus lycii powder; 1-20% of hippophae rhamnoides powder; and, optionally, a pharmaceutically-acceptable excipient.

30. An herbal composition of claim 28, wherein said composition is effective to enhance levels of blood oxygen, to enhance working capacity and endurance, to enhance memory and concentration, to reduce stress, to enhance cardiac and cardiovascular function, to provide antioxidant effects, to modulate testosterone levels, to modulate sleep, to improve sexual performance.

2. Document ID: US 20020119933 A1

L5: Entry 2 of 6 File: PGPB Aug 29, 2002

DOCUMENT-IDENTIFIER: US 20020119933 A1
TITLE: Compositions and methods for improving cardiovascular function

Abstract Paragraph (1):
The present invention relates to compositions for supplementing the diet of subjects suffering from cardiovascular or peripheral vascular disease or those at risk for such conditions. Ribose is given alone or in combination with one or a combination of vasodilators, nutrients and vitamins. Preferred vitamins include Vitamins C, B6, B12 and folic acid. Preferred nutrients include glutamine and glucose.

Summary of Invention Paragraph (3):
[0004] Often, persons who consider themselves to be in good health with a good nutritional status are actually somewhat suboptimal in both parameters, rendering them at risk for developing such medical conditions. Dietary supplements, functional or medical foods developed for improving cardiovascular function may also benefit such persons as cardioprotectors.

Summary of Invention Paragraph (4):
[0005] In the area of medically recommended supplementation artificial diets have played a key role for many years. Post-surgery, the gastro-intestinal tract of a patient is typically unable to properly digest food for several days. In such cases parenteral nutrition is essential, wherein the patient is given glucose or a carefully formulated mixture of salts, carbohydrates, amino acids, fatty acids, and vitamins. Even after the patient is weaned from parenteral nutrition, enteral nutrition with a similar composition may be established orally or via a feeding tube, or a medical food enteral supplement may be added to his or her diet in order to optimize the types and amounts of nutrients the patient requires and receives.

Summary of Invention Paragraph (5):
[0006] The most pressing need for improved prevention, rehabilitation and maintenance regimens is in the area of cardiovascular disease, which is the leading cause of death worldwide. It has been projected that one of five persons in the United States has cardiovascular disease. Within this arena, myocardial infarction accounts for more than half a million deaths per year. Furthermore, survivors face a level of morbidity and subsequent disability that affects their medical, social, and of equal importance, economic status. Therefore, surviving the initial acute event of a myocardial infarction leaves patients with a variety of challenges. Such patients may be left in a state of compromised cardiovascular function such as chronic ischemic disease, congestive heart failure or reduced peripheral blood flow.

Summary of Invention Paragraph (15):
[0015] According to the methods of this invention, D-Ribose (which may be subsequently referred to as "ribose") is administered to a patient at least once a day in unit dosages of from two to ten grams. A preferred method is the administration of a unit dosage of two to eight grams of ribose two or three times a day. The most preferred method is the administration of a unit dosage of five grams of ribose given three times per day. The unit dosage may be dissolved in a suitable amount of water or may be ingested as a powder.

Summary of Invention Paragraph (16):

[0016] Compositions comprising a vasodilator and ribose are provided. Ribose in a unit dosage of one to 20 grams is administered with an effective amount of a vasodilator. A more preferred dosage of ribose is two to ten grams. A most preferred dosage of ribose is five grams. The vasodilator may be L-arginine, nitroglycerine, nitrates, nitrites, papaverine, isoproterenol, nylidrin, isoxsuprine, nitroprusside, adenosine, xanthine, ethyl alcohol, dipyramide, hydrazaline, minoxidil, diazoxide or analogs of the foregoing. A most preferred vasodilator is L-arginine. The components may be mixed together in a powder for simultaneous administration. When the vasodilator is nitroglycerine, a nitrate or a nitrite, ribose is preferably administered orally about fifteen minutes before the vasodilator is given buccally, sublingually or transdermally. This composition is administered from one to four times daily.

Summary of Invention Paragraph (17):
[0017] Compositions comprising ribose and vitamins are provided. Ribose in a unit dosage of one to 20 grams is administered along with one or more of vitamins C, B6, B12 and/or folic acid. It is most convenient to prepare ribose and vitamins as a triturated powder. A more preferred unit dosage of ribose to be administered with vitamins is two to 10 grams of ribose. A most preferred unit dosage of ribose to be administered with vitamins is five grams of ribose.

Summary of Invention Paragraph (18):
[0018] Compositions comprising ribose, a vasodilator and vitamins are provided. Ribose in a unit dosage of one to 20 grams is administered along with a vasodilator and one or more of vitamins C, B6, B 12 and/or folic acid. It is most convenient to prepare ribose, a vasodilator and vitamins as a triturated powder. A more preferred unit dosage of ribose to be administered with a vasodilator and vitamins is two to 10 grams of ribose. A most preferred unit dosage of ribose to be administered with vitamins is five grams of ribose. A most preferred composition comprises ribose, L-arginine, and/or folic acid.

Summary of Invention Paragraph (19):
[0019] Glutamine may be added to each of the above compositions. Dextrose may be added to each of the above compositions in the same amount as ribose, if it is desired to eliminate potential hypoglycemia. L-Carnitine may be added to each of the above compositions. Taurine may be added to each of the above compositions. Creatine may be added to each of the above compositions. Pyruvate may be added to each of the above compositions. Coenzyme Q10 may be added to each of the above compositions.

Summary of Invention Paragraph (20):
[0020] A most preferred composition is provided comprising ribose, L-arginine, glutamine, folic acid, glucose, vitamins B12, B6 and C. Ornithine, citrulline or other orally administered vasodilators may be added in place of or in addition to L-arginine. Any one or a combination of L-carnitine, taurine, creatine, pyruvate may be added to the above compositions

Summary of Invention Paragraph (21):
[0021] Any of the compositions of this invention are preferably dissolved in about eight ounces of water and ingested as a solution. Flavorings and other additives may be added to make the solution more palatable. In each of the compositions of this invention, D-ribose in a unit dosage of one to 20 grams is administered two to four times per day. The other ingredients may vary in accordance with recommended daily allowance.

Summary of Invention Paragraph (23):
[0022] The invention comprises compositions that include D-ribose, alone and in combination with a vasodilator. Nutrients that improve cardiovascular function, healing, or have other healthful characteristics are also provided. Those nutrients selected will have effects on metabolic pathways or physiological functions different from those of ribose and thus will have incremental benefit over the basic benefit of ribose alone. Improvement of cardiovascular function results inherently in improvement of a subject's physical capability and hence enhances the subject's quality of life. Therefore, in the present invention, when the term "cardiovascular function" is used, it is understood to include improvement of physical capability and enhancement of quality of life. Nutrients to be used in this invention in

combination with D-ribose include, but are not limited to those that may enhance endothelium-dependent vasodilation by acting on nitric oxide release including ascorbic acid, L-arginine, ornithine, citrulline, glutamine, folic acid, vitamin B6 and vitamin B12. Also included are other energy enhancing compounds such as L-carnitine, pyruvate, taurine, and coenzyme Q10.

Summary of Invention Paragraph (24):
[0023] D-ribose (otherwise referred to as ribose) is a natural 5-carbon sugar found in every cell of the body. It forms part of the backbone of the genetic materials ribonucleic acid and deoxyribonucleic acid as well as part of the basic structure of the body's main energy carrying molecule, adenosine triphosphate (ATP).

Summary of Invention Paragraph (27):
[0026] Because of its ability to enhance ATP recovery and synthesis ribose can increase exercise capacity in both ill and healthy people. One study found that orally administered high doses of ribose increased the treadmill performance of angina patients (Pliml et al 1992). Another study found that in athletes on exercise bikes, power output was greater in the group that was taking supplemental ribose (U.S. Pat. No. 6,159,942).

Summary of Invention Paragraph (28):
[0027] Ribose is the key ingredient in the compositions described in this invention. Other energy enhancers might be included that increase the effect of ribose. Nutrients that act by other mechanisms can be energy enhancers that would optimize the nutritional composition. For example, increasing a vessel's diameter would enable blood to reach outlying muscle tissue and thus transport ribose and nutrients to that tissue. Enhancement of other physiological functions in addition to energy would compound the effect of the nutritional composition.

Summary of Invention Paragraph (31):
[0030] Several nutrients have a positive influence on NO production. Those that are described here are relevant to the invented composition and include ascorbic acid, L-arginine, ornithine, glutamine, and folic acid.

Summary of Invention Paragraph (41):
[0040] Normally, a wholesome diet is considered to provide sufficient amounts of these nutritive elements. Supplementation with off-the-shelf multivitamins is common. However, patients requiring improvement in cardiovascular function or peripheral vascular function often are not able or willing to prepare or choose a diet that will meet their enhanced requirements for these nutritive elements, nor do the usual vitamin supplementations provide sufficient levels for this group of patients. Therefore, it is of increased benefit to add at least these vitamins to the compositions of this invention.

Detail Description Paragraph (2):
[0042] Pliml (1992) has previously reported that 60 grams of D-Ribose daily in four 15 gram doses taken for three days benefitted patients with cardiovascular disease. This dosage of ribose may bring on hypoglycemia with concomitant dizziness, nausea and sweating. Subjects frequently experience abdominal distress and diarrhea similar to that in individuals with lactose intolerance who ingest milk. Because of these unpleasant side effects, patients will be reluctant to continue ribose on a maintenance basis. Therefore, a study was done to select a lower and safer dose of ribose that is effective in increasing cardiovascular and peripheral vascular function and can be taken long-term for maintenance and cardioprotection.

Detail Description Paragraph (4):
[0044] A double-blinded, randomized, crossover clinical study was initiated to determine whether patients with cardiovascular disease could find a ribose benefit at lower, safer doses. Patients with known chronic coronary artery disease with stable angina pectoris and chronic heart failure, class II and III (New York Classification, NYHA) were selected for the study. All patients had a history and ongoing occurrences of angina pectoris. All but two patients had a previous history of myocardial infarction, with one-third having two or more previous infarcts. Thirty-one percent of the patients had a previous history of surgical intervention, either coronary artery bypass graft (CABG) or angioplasty. All patients were being

treated with nitrates, molsidim and beta blockers. Three patients were also on diltiazem and an additional three on trapidil. Medications were not altered during the study. Exclusion criteria included patients <18 years of age, those with severe concurrent disease (renal failure, diabetes mellitus, neoplasia), evidence of hyperthyroidism and inability to follow the protocol.

Detail Description Paragraph (5):
[0045] The study consisted of two treatment periods, three weeks in duration. Initially, either ribose or placebo (dextrose) was administered three times a day with meals. Five grams of either ribose of placebo was dissolved in approximately eight ounces of fluid shortly before administration. Following the initial treatment period, the patients were given no ribose or placebo treatment for one week as a washout period. The patients were then given the alternate treatment for three weeks for the crossover phase of the study.

Detail Description Paragraph (15):
[0055] Analysis of variance for repeated measures (ANOVA) was used for the analysis of serial changes of continuous parameters within and between the randomized, assigned treatment arms, i.e. ribose vs placebo. Further comparison were subject to Bonferroni correction. In all cases, a p value .ltoreq.0.05 was considered statistically significant.

Detail Description Paragraph (18):
[0058] ECHO revealed a significant improvement in deceleration time of the E wave (Edc in msec), stroke volume index (SVI, ml/body mass index) ejection fraction (EF, %), atrial contribution (Ac, &), and left ventricular systolic volume (LVVs, ml) in the ribose. Analysis of parameters reflecting diastolic function revealed significant findings. Ribose demonstrated a significant shorter deceleration time of the E wave, with a significantly smaller left atria volume and a higher atrial contribution to left ventricular filling as compared to patients treated with placebo.

Detail Description Paragraph (20):
[0060] On the other hand, a noted difference in quality of life and physical functioning was observed between modalities. Patients receiving oral ribose demonstrated a significant improvement in the overall score of the quality of life index. This increase was paralleled by a significant improvement in physical function..

Detail Description Paragraph (21):
[0061] Over a relatively short term, treatment with oral D-ribose significantly improved diastolic cardiac function in patients with severe coronary artery disease and congestive heart failure. Administration of ribose resulted in an enhanced quality of life. Longer term studies with ribose supplementation and studies on less severely ill patients are expected to show greater improvement in diastolic and systolic function. In the absence of adverse effects, it is recommended that patients continue on a maintenance method of at least one dose of ribose daily.

Detail Description Paragraph (23):
Compositions Of Ribose With Other Components

Detail Description Paragraph (24):
[0062] It has been shown in other studies that the beneficial effects of ribose are augmented in subjects with poor circulation by the concomitant administration of vasodilators, which relax the blood vessels, allowing better circulation and hence better accessibility of ribose to the tissues. It can be noted in Example 1 that these severely ill patients are all taking at least one vasodilator. Nitrates, especially nitroglycerine, are most commonly used because of their rapid onset of action. Patients experiencing angina self-administer nitrates buccally, sublingually or transdermally, since nitrates administered orally are quickly cleared on passage through the liver. Even when administered in this manner, nitrates have a very short half-life in the body. Nitrates are not a pleasant therapy, often causing severe headaches. It is beneficial to administer a vasodilator with ribose in order improve circulation, thereby making ribose more available to the tissues. Ribose is most conveniently administered orally. Therefore, in order to have the maximum benefits

in subjects in which the vasodilator cannot be administered orally, it is advised to ingest ribose about fifteen minutes before administration of the vasodilator. This minor inconvenience may be eliminated when the vasodilator selected may be administered orally. Therefore, the compositions below incorporate L-arginine or its equivalents as a vasodilator. Other useful orally administered vasodilators include L-arginine, nitroglycerine, nitrates, nitrites, papaverine, isoproterenol, nylidrin, isoxsuprine, nitroprusside, adenosine, xanthine, ethyl alcohol, dipyramide, hydrazaline, minoxidil, diazoxide or analogs of the foregoing.

Detail Description Paragraph (28):
[0066] The ingredients are triturated as a dry powder. The powder can be conveniently dissolved in any carrier, preferably one that comprises a pleasant flavoring and color. Many patients will prefer a sweeter composition. Sweeteners such as sucrose or corn syrup or the like can easily be added to taste. It may be most convenient to prepare a concentrated liquid solution to be diluted by the patient with water or other liquid.

Detail Description Paragraph (31):
[0067] Any of the above compositions, or ribose alone, can be supplemented with one or any combination of L-carnitine, taurine, creatine, coenzyme Q10, and/or pyruvate. Supplementation with any or all of these compounds will incrementally improve cardiovascular or peripheral vascular function and provide cardioprotection against onset or recurrence of cardiovascular or peripheral vascular disease..

Detail Description Paragraph (33):
[0068] The following study was devised to check the benefits of additions to the basic ribose treatment.

Detail Description Paragraph (46):
[0081] After baseline assessment and randomization, as a pilot study, four patients at each site will begin oral supplementation with Composition B. Four patients at each site will be given a placebo consisting of 5 g glucose. The supplementation will be taken twice a day, around mealtime. All patients will discontinue supplementation after eight weeks. During the supplementation period, at week eight and each week for two weeks following discontinuation of exercise assessment, patients will undergo an evaluation consisting of exercise assessment and a quality of life questionnaire. In addition, any non-insulin dependent diabetics will have daily serum glucose levels drawn for the first weeks after beginning oral supplementation.

Detail Description Paragraph (48):
[0083] It is expected that the patients given the composition of this invention will be able to exercise longer, at a higher level and without restraint or cardiac symptoms than in those patients receiving placebo. It is further expected that the reported quality of life will be more favorable in the patients receiving the composition of this invention than in those receiving placebo.

Detail Description Paragraph (51):
[0084] As shown in Example 1, treatment with ribose improves diastolic cardiac function. Since hypertension is accompanied by left ventricular dysfunction, it is expected that the administration of ribose to patients experiencing hypertension with result in a benefit. One subject has been tested. Her blood pressure has been tested at borderline values of 130/90. Following daily administration of ribose at 5-10 grams per day, her blood pressure was lowered to as low as 108/78. Further studies with ribose alone or with Composition A are expected to confirm the pressure-lowering effects of ribose administration.

Detail Description Table CWU (1):
1TABLE I THERAPY Edc* SVI* EF Ac # LVVs* Ribose 193.5 .+-. 45.9 2.63 .+-. .57 51.0 .+-. 7.3 45.3 .+-. 9.2 64.4 .+-. 24.8 Dextrose 250 .+-. 70.2 1.99 .+-. .71 40.9 .+-. .71 39.2 .+-. 9.7 78.4 .+-. 27.0 *(p .ltoreq. .005, #p < .01)

Detail Description Table CWU (2):
2 COMPOSITION A PREFERRED DOSE ACCEPTABLE RANGE D-ribose 5 g 1-20 g L-arginine 2 g 0*-8 g *arginine can be replaced by citrulline or ornithine or other orally

administered vasodilators

Detail Description Table CWU (3):
3 COMPOSITION B PREFERRED DOSE ACCEPTABLE RANGE D-ribose 5 g 1-20 g Glucose 5 g 0-20 g (to equal ribose amount) L-arginine 2 g 0*-8 g Glutamine 500 mg 40-1000 mg Vitamin C 500 mg 100-1000 mg Folic acid 0.2 mg 0.1-1.0 mg Vitamin B12 0.25 mg 0.1-1.0 mg Vitamin B6 6 mg 1-50 mg *arginine can be replaced by citrulline or ornithine or other orally administered vasodilators

CLAIMS:

1. A method for improving cardiovascular function of a subject comprising the administration of two to ten grams of D-ribose one to four times daily to the subject.

2. The method of claim 1 wherein three to five grams of D-ribose is administered one to four times daily to the subject.

3. The method of claims 1 or 2 wherein D-ribose is administered one to four times daily for at least one week.

4. A composition for improving cardiovascular function of a subject comprising administering an effective amount of D-ribose in combination with a vasodilator to the subject.

5. The composition of claim 4 wherein the effective amount of D-ribose is one to 30 grams and the vasodilator is L-arginine, nitroglycerine, a nitrate, a nitrite, papaverine, isoproterenol, nylidrin, isoxsuprine, nitroprusside, adenosine, xanthine, ethyl alcohol, dipyramide, hydrazaline, minoxidil or diazoxide.

6. The composition of claim 4 wherein the effective amount of D-ribose is two to 10 grams.

7. The composition of claim 4 wherein the effective amount of D-ribose is three to eight grams.

8. The composition of claim 4 further comprising at least one of glucose, glutamine, Vitamin C, Vitamin B6, Vitamin B12, folic acid.

9. The composition of claims 4 or 8 further comprising at least one of L-carnitine, taurine, creatine, Coenzyme Q10 or pyruvate.

11. A composition for improving cardiac function in a subject comprising: one to 20 grams of D-ribose; 0 to 20 grams of glucose; one to eight grams of L-arginine; 100 to 1000 milligrams of Vitamin C; 0.1 to one milligrams of folic acid; 0.1 to one milligrams of Vitamin; and one to 50 milligrams of Vitamin B6.

12. A composition for improving cardiac function in a subject comprising: five grams of D-ribose; five grams of glucose; two grams of L-arginine; 500 milligrams of Vitamin C; 0.2 milligrams of folic acid; 0.25 milligrams of Vitamin B 12; and six milligrams of Vitamin B6.

15. The method of claims 4, 10 or 13 wherein the vasodilator is nitroglycerine, a nitrate, a nitrite, or nitroprusside, and the D-ribose is ingested orally fifteen minutes before the vasodilator is administered sublingually, buccally or transdermally.

16. A method of reducing blood pressure of a subject comprising administering D-ribose to the subject.

17. The method of claim 16 wherein D-ribose or any one of the compositions of claims 5,6,7,8,9,10,11 or 12 is administered to the subject one to four times per day.

3. Document ID: US 20020072072 A1

L5: Entry 3 of 6 File: PGPB Jun 13, 2002

DOCUMENT-IDENTIFIER: US 20020072072 A1
TITLE: ADP-glucose receptor

Brief Description of Drawings Paragraph (4):
[0013] FIG. 2A shows changes in intracellular calcium concentration in CHO cells transiently transfected with G.alpha.16 and G.alpha.qi3 in response to ADP-glucose (filled squares), ADP-ribose (open circles), or ADP-mannose (open triangles) and in untransfected CHO cells in response to ADP-glucose (closed triangles).

Brief Description of Drawings Paragraph (5):
[0014] FIG. 2B shows changes in intracellular calcium concentration in untransfected HEK 293 cells in response to ADP-glucose (filled squares), ADP-ribose (open circles) or ADP-mannose (open triangles). Values are mean .+-.S.E.M. (n=3) from a representative experiment.

Detail Description Paragraph (2):
[0024] The invention relates to the identification of ADP-glucose and ADP-ribose as signal transmitters in mammals. The invention further relates to the identification of an ADP-glucose receptor and characterization of its signal transduction pathway and physiological activity. Thus, compositions and methods useful for identifying ligands, agonists and antagonists of ADP-glucose receptor are provided. Such compounds can be used therapeutically to prevent or ameliorate conditions associated with altered ADP-glucose receptor function, including conditions associated with smooth muscle contractility and vascular tone. Also provided are compositions and methods useful for diagnosing or predicting susceptibility to conditions associated with altered ADP-glucose receptor function. Such knowledge allows optimal medical care for an affected individuals, including appropriate genetic counseling and prophylactic and therapeutic intervention.

Detail Description Paragraph (6):
[0028] An ADP-glucose receptor is also characterized by its ability to transduce a G-protein coupled signal in response to the nucleoside sugar ADP-ribose, although with an EC.sub.50 about 10-fold higher than for ADP-glucose. An ADP-glucose receptor is further characterized in that it does not transduce a G-protein coupled signal in response to ADP-mannose, or transduces such a signal with an EC.sub.50 at least 100-fold, such as at least 1000-fold, higher than for ADP-glucose.

Detail Description Paragraph (61):
[0083] The invention also provides an isolated ADP-glucose receptor polypeptide. The invention polypeptides are useful for a variety of applications, such as to identify ADP-glucose receptor ligands, agonists and antagonists, or as negative controls to confirm the specificity of known or presumptive ligands, agonists and antagonists of other G-protein coupled receptors. For such applications, the invention polypeptides are preferably contained within a composition containing a cell or artificial membrane, and components such as ADP-glucose or a G-protein. The invention polypeptides can also advantageously be used to prepare antibodies, which can be administered therapeutically as ADP-glucose receptor antagonists, or used as diagnostic reagents.

Detail Description Paragraph (78):
[0100] An example of the method is described in Example I, below, in which an ADP-glucose receptor polypeptide, recombinantly expressed in CHO cells coexpressing G.alpha.16 and G.alpha.qi3, was contacted separately with ADP-glucose, CDP-glucose,

GDP-glucose, UDP-glucose, TDP-glucose, ADP-ribose, ADP-mannose, AMP, ADP, ATP, and adenosine, to determine the ability of each compound to alter production of a G-protein coupled signal (ie. increase intracellular Ca.sup.2+ concentration). By this assay, ADP-ribose was determined to be a partial agonist of ADP-glucose receptor (see FIG. 1A). The antagonistic effect of a compound can likewise be determined under the same exemplary conditions, but with the candidate compound added prior to addition of ADP-glucose at about its EC.sub.50 concentration, and the effect of the candidate compound on inhibiting the agonist-induced increase in intracellular Ca.sup.2+ concentration determined.

Detail Description Paragraph (94):
[0116] A method of identifying ADP-glucose receptor agonists and antagonists can be performed either in the presence of a known ADP-glucose receptor agonist (e.g. ADP-glucose or ADP-ribose), or in the absence of agonist. When present, the agonist concentration is preferably within 10-fold of the EC.sub.50 under the assay conditions. Thus, an agonist that competes with ADP-glucose or ADP-ribose for signaling through the ADP-glucose receptor, or indirectly potentiates signaling, can be readily identified. Likewise, an antagonist that prevents ADP-glucose or ADP-ribose from binding its receptor, or indirectly decreases signaling, can also be identified. Such compounds that demonstrate agonistic and antagonistic effects in the presence of ADP-glucose are particularly useful for therapeutic applications, in which physiological concentrations of circulatory ADP-glucose or ADP-ribose are likely to be present.

Detail Description Paragraph (102):
[0124] ADP-glucose itself, and the ADP-glucose receptor agonists (e.g. ADP-ribose) and antagonists identified using the methods and compositions described herein, are therapeutic compounds that can be administered to an individual, such as a human or other mammal, in an effective amount to increase or decrease signaling through the ADP-glucose receptor, and thus to prevent or ameliorate a ADP-glucose receptor associated condition.

Detail Description Paragraph (106):
[0128] Additionally, smooth muscle tone is necessary for the function of vascular tissues. As described herein, signaling through the ADP-glucose receptor induces vasorelaxation in rat arterial tissue preparations. Therefore, the ADP-glucose receptor agonists or antagonists can be used to modulate vascular smooth muscle function by acting as vasoconstrictors or vasodilators. Conditions in which agents that act as vasoconstrictors or vasodilators are beneficial include disorders of cardiovascular function such as ischemia, hypertension, hypotension, angina pectoris, myocardial infarction, stroke, congestive heart failure, shock, erectile dysfunction, orthostatic intolerance, and migraine.

Detail Description Paragraph (107):
[0129] Consistent with the determination that signaling through the ADP-glucose receptor affects vascular function, it has recently been reported that cyclic perfusion of ADP-ribose, disclosed herein to be an ADP-glucose receptor agonist, in isolated frog heart induces a dose-dependent decrease in heart rate and contraction force, as well as a decrease in the action potential duration and rate of rise in the sinus node. Additionally, systemic administration of ADP-ribose to unanesthetised frogs induced a reversible increase in heart rate, likely due to sympathetic effects (Sosulina et al., Ross Fiziol Zh Im I M Sechenova 85:508-514 (1999); English abstract).

Detail Description Paragraph (113):
[0135] In plants and bacteria the formation of ADP-glucose is catalyzed by ADP-glucose pyrophosphorylase, which can also hydrolyze ADP-glucose depending on the concentration equilibrium. A related enzyme has recently been cloned from human and rat, termed YSA1H or NUDT5, which has a very similar tissue distribution of expression as ADP-glucose receptor (Gasmi et al., Biochem. J. 344:331-337 (1999); Yang et al., J. Biol. Chem. 275:8844-8853 (2000)). NUDT5 could therefore play a role in the synthesis or degradation of ADP-glucose and/or ADP-ribose as transmitters. Therefore, ADP-glucose receptor agonists and antagonists can be used to prevent or treat conditions associated with abnormal expression or function of YSA1H or NUDT5, and with physiological responses thereto.

Detail Description Paragraph (116):
[0138] In one embodiment, the invention provides a method of ameliorating an ADP-glucose receptor associated condition by administering to an individual an effective amount of a therapeutic composition comprising ADP-glucose, or an ADP-glucose receptor agonist or antagonist. As described in Examples II and III, below, ADP-glucose induces inhibits contractile responses in guinea pig ileum and induces vasorelaxation in rat arterial tissues. Therefore, ADP glucose or an ADP-glucose receptor agonist or antagonist can be used, for example, to treat disorders involving smooth muscle contraction, including disorders of cardiovascular function, by inducing or inhibiting relaxation or constriction of the affected smooth muscle, as warranted by the particular condition.

Detail Description Paragraph (117):
[0139] The efficacy of a therapeutic compound of the invention in treating an ADP-glucose receptor associated condition can be determined using credible animal models of human disease, which are well known in the art, or using normal animals. For example, animal models of cardiovascular disorders, such as pulmonary hypertension, congestive heart failure, and the like, are available. The efficacy of a therapeutic compound in ameliorating a cardiovascular condition can be determined by administering the compound to the animal and determining the effect of the compound on an index of cardiovascular function correlated with the disease state, or the effect of the compound on ameliorating the disease state.

Detail Description Paragraph (118):
[0140] Exemplary indices of cardiovascular function that can be measured to determine the effect of a therapeutic compound include systemic arterial pressure, pulmonary arterial pressure, and heart rate. Such indices can be measured at a particular endpoint, or can be measured continuously. A radiotelemetry system, such as the system described in Mills et al., J. Appl. Physiol. 88:1537-1544 (2000), can advantageously be used to continuously monitor blood pressure and heart rate in freely moving animals, and thus to determine the effect of the therapeutic compound on such indices. Those skilled in the art understand which indices of function, and which animal models, are correlated with human ADP-glucose receptor associated conditions.

Detail Description Paragraph (122):
[0144] Preferably, the therapeutic compounds are administered to a subject as a pharmaceutical composition comprising the compound and a pharmaceutically acceptable carrier. The choice of pharmaceutically acceptable carrier depends on the route of administration of the compound and on its particular physical and chemical characteristics. Pharmaceutically acceptable carriers are well known in the art and include sterile aqueous solvents such as physiologically buffered saline, and other solvents or vehicles such as glycols, glycerol, oils such as olive oil and injectable organic esters. A pharmaceutically acceptable carrier can further contain physiologically acceptable compounds that stabilize the compound, increase its solubility, or increase its absorption. Such physiologically acceptable compounds include carbohydrates such as glucose, sucrose or dextrans; antioxidants, such as ascorbic acid or glutathione; chelating agents; and low molecular weight proteins.

Detail Description Paragraph (131):
[0153] A variety of assays, and a variety of ligand probes can be used to detect expression of an ADP-glucose receptor in a test sample. Exemplary ligand probes include the antibodies of the invention, detectably labeled ADP-glucose or ADP-ribose, and the agonists, antagonists and ligands identified by the methods described herein. The choice of assay format and ligand probe will depend on the alteration it is desired to identify.

Detail Description Paragraph (149):
[0169] To enforce coupling of the novel receptor to the phospholipase C pathway, CHO cells were transiently cotransfected with expression constructs containing the amplified receptor DNA, G.alpha.16 and a chimeric G.alpha.q subunit carrying the C-terminal tail of G.alpha.i3. From among ADP-glucose, CDP-glucose, GDP-glucose, UDP-glucose, TDP-glucose, ADP-ribose, AMP, ADP, ATP, and adenosine (all obtained from Sigma), and ADP-mannose (a gift of Drs. H. Yang and J. H. Miller, University of

California, Los Angeles), only ADP-glucose and ADP-ribose induced a dose-dependent and transient increase in intracellular Ca.sup.2+ ([Ca.sup.2+].sub.i) levels in transfected but not in untransfected cells.

Detail Description Paragraph (150):
[0170] As shown in FIG. 2, ADP-glucose induced a transient increase in [Ca.sup.2+].sub.i with an EC.sub.50 of 2.98.+-.0.22 .mu.M in CHO cells transiently transfected with the receptor construct together with G.alpha.16 and G.alpha.qi3 (FIG. 2A, filled squares). The closely related molecule ADP-ribose could also activate the transfected receptor specifically, although less potently in the same assay (FIG. 2A, open circles; EC.sub.50=59.4.+-.7.3 .mu.M). ADP-mannose was unable to activate the receptor, although mannose and glucose are epimers, differing only in the spatial orientation of one hydroxyl group. Dose-response curves were calculated using GraphPad Prism (GraphPad Software Inc.).

Detail Description Paragraph (155):
[0175] In contrast to CHO cells, ADP-ribose behaved as a full agonist and potently increased in HEK 293 cells with an EC.sub.50 of 38.7.+-.10.6 .mu.M (FIG. 2B, open circles). This discrepancy could reflect the different subsets of G proteins expressed in the two cell lines, enabling a more efficient coupling of the receptor in HEK 293 versus CHO cells.

Detail Description Paragraph (167):
[0185] ADP-glucose dose-dependently inhibited electrically evoked contractions with an EC.sub.50 value of 6.64.+-.0.4 .mu.M (FIGS. 4B and 5A). Maximally effective concentrations of ADP-glucose produced 90% inhibition. ADP-ribose produced very similar inhibitory effects on electrically-evoked contractions in these preparations, whereas other nucleoside-diphosphoglucoses were ineffective.

CLAIMS:

22. A method of ameliorating an ADP-glucose receptor associated condition, comprising administering to an individual an effective amount of a therapeutic composition comprising ADP-glucose, or an ADP-glucose receptor agonist or antagonist.

23. The method of claim 22, wherein said ADP-glucose receptor associated condition is a disorder of cardiovascular function.

24. The method of claim 22, wherein said therapeutic composition induces vasorelaxation.

25. A composition, comprising an isolated ADP-glucose receptor polypeptide and ADP-glucose.

26. The composition of claim 25, wherein said ADP-glucose receptor polypeptide has at least 70% identity to the amino acid sequence designated SEQ ID NO:2.

27. The composition of claim 25, wherein said ADP-glucose receptor comprises the amino acid sequence designated SEQ ID NO:2.

28. The composition of claim 25, wherein said ADP-glucose is a detectably labeled ADP-glucose.

29. The composition of claim 28, wherein said detectably labeled ADP-glucose is radiolabled ADP-glucose.

30. The composition of claim 25, wherein said polypeptide is contained in a lipid bilayer.

31. The composition of claim 30, further comprising a G-protein.

32. The composition of claim 31, wherein said G-protein comprises a G.alpha. subunit selected from the group consisting of G.alpha.q, G.alpha.16 and a chimeric G.alpha..

33. The composition of claim 30, wherein said lipid bilayer is a cell membrane.

☐ 4. Document ID: US 20020013256 A1

L5: Entry 4 of 6 File: PGPB Jan 31, 2002

DOCUMENT-IDENTIFIER: US 20020013256 A1
TITLE: Novel inhibitors of formation of advanced glycation endproducts (AGES)

Summary of Invention Paragraph (2):
[0002] The present invention relates generally to the modification and aging of proteins through reaction with glucose and other reducing sugars, such as fructose or ribose and more particularly to the inhibition of nonenzymatic glycation of proteins which often results in formation of advanced glycation endproducts and crosslinks.

Brief Description of Drawings Paragraph (4):
[0027] FIG. 3 shows the inhibition by LR93-LR102 in the G.K. Peptide-Ribose Assay. The bars are the same as for FIG. 2.

Detail Description Paragraph (3):
[0042] The mechanism(s) by which this class of compounds inhibits glycation, AGE-formation, and crosslinking is yet to be known. The present study indicates that these compounds are powerful inhibitors that act at multiple steps of glycation and AGE-formation, i.e., early stage, as evidenced by lowering HbAlc levels in the .delta.-Glu assay, a specific assay for the early stage of glycation (type A or B inhibitor). Most of these compounds strongly inhibit the post-Amadori glycation as demonstrated by the BSA-glucose and G.K.-Ribose assays (type D inhibitors), and a good number of them are powerful inhibitors of AGE protein crosslinking, as evidenced by a specific ELISA assay (type E inhibitors as described by Baynes Classification (Khalifah et al., 1999)).

Detail Description Paragraph (24):
N-Acetyl-Glycyl-Lysine Methyl Ester (G.K. Peptide)-Ribose Assay

Detail Description Paragraph (25):
[0056] Evaluation of the late glycation products (AGEs), and AGE-inhibition by the new inhibitor compounds was tested by incubation of G.K. peptide in ribose in the presence or the absence of the agent, followed by determination of chromophores generated in the course of glycation and AGE formation through determination of their specific fluorescence. The Nagaraj et al. (1996) method used to evaluate the ability of the compounds of the present invention to inhibit the crosslinking of N-acetylglycyl-lysine methyl ester in the presence of ribose was as follows:

Detail Description Paragraph (29):
[0060] Ribose 800 mM (120 mg/mL) in 0.5 M phosphate buffer

Detail Description Paragraph (31):
[0062] FIG. 3 shows the inhibitory effects of the compounds to block specific fluorescence of protein-AGE in these separate determinations, using G.K. peptide-ribose assay. Results are shown in Table 3. The results of this assay indicate that all ten compounds investigated here have strong inhibitory effects and block specific fluorescence of proteins AGE in these separate determinations.

Detail Description Paragraph (51):

[0079] Bucala R and Rahbar S (1998). Protein Glycation and Vascular Disease in Endocrinology of Cardiovascular Function. Edited by E. R. Levin and J. L. Nadler, Kluwer Acad. Publishers, pp. 159-180.

Detail Description Table CWU (3):
3TABLE 3 Percent Inhibition by LR93-LR102 in the G.K.-Ribose Assay Compound Percent Inhibition AG 67 LR93 42.8 LR94 33.7 LR95 29.5 LR96 42.4 LR97 33.3 LR98 37.3 LR99 39.5 LR100 28.5 LR101 40.1 LR102 35.1

CLAIMS:

7. A pharmaceutical composition comprising an effective amount of i) a compound or a pharmaceutically acceptable salt of said compound and ii) a pharmaceutical carrier, wherein said compound is a compound of claim 6.

☐ 5. Document ID: US 6399116 B1

L5: Entry 5 of 6 File: USPT Jun 4, 2002

DOCUMENT-IDENTIFIER: US 6399116 B1
TITLE: Rhodiola and used thereof

Abstract Text (1):
The present invention relates to Rhodiola, preferably Rhodiola crenulata, to treat various conditions and diseases in mammals. Rhodiola crenulata is a Tibetan herb which has been discovered to have highly useful and beneficial properties heretofore unknown. Rhodiola crenulata is especially preferred to enhance blood oxygen levels, to enhance working capacity and endurance, to enhance memory and concentration, to enhance cardiac and cardiovascular function, to provide antioxidant effects, to protect against oxidation, to modulate testosterone and estradiol levels, to modulate sleep, and to enhance sexuability, such as improve sexual performance.

Brief Summary Text (2):
The present invention relates to compositions, articles of manufacture, extracts, compounds, methods of use, methods of treatment, methods of preparation, etc., which relate to plants of the genus Rhodiola, preferably Rhodiola crenulata, which have a variety of useful and beneficial effects, including, e.g., to enhance blood oxygen and nutrients levels, e.g., through enhancing oxygen transport, to enhance working capacity and endurance, to reduce muscle fatigue, to enhance memory and concentration, to reduce stress, to enhance cardiac and cardiovascular function, to provide antioxidant effects, to protect against oxidation, to provide anti-cancer effects, to promote DNA repair, to provide anti-radiation effects, to protect against radiation, to reduce inflammation, to increase insulin, to decrease levels of glucagon, to reduce histamine release, to reduce allergic reactions, preferably, to modulate testosterone levels, and to modulate sleep, especially to promote sleep, to modulate blood lipids, preferably, e.g., to lower cholesterol levels, to promote weight loss, and to enhance sexuability, such as improve sexual performance.

Brief Summary Text (4):
Rhodiola is a diverse genus of plants which includes more than 50 different species, including, e.g., algida, arctica, crenulata, elongata, gelida, imbricataishidae, iremelica, kirilowii, linearifolia, phariensis, pinnatifida, quadrifida, aff. quadrifida, rosea, sachalinensis, and wolongensis. These species vary from each other widely, differing in, e.g., chromosome number (e.g., Makoto et al., Journal of Japanese Botany, 70(6):334-338, 1995), chemical composition, morphology, medicinal properties, developmental stages (e.g., Ishmuratatova and Satsyperova, Rastitel'nye

Resursy., 34(1):3-11, 1998), geographical distribution, etc. Scientific studies (e.g. Peng et al, Chinese Herb Medicine (1995), 26(4): 177-179, and Wang et al, Acta Phrmaceutica Sinica(1992), 27(2): 117-120) indicate constituents of Rhodiola crenulata include, e.g., salidroside, tyrosol, .beta.-sitosterol, gallic acid, pyrogallol, crentulatin, rhodionin, rhodiosin, among which, crenulatin, e.g., is found only in R. crenulata and has not been found in any other Rhodiola species. Rhodiosin and rhodionin exists in some, but not all, Rhodiola species.

Brief Summary Text (11):
Rhodiola can also be formulated with other active ingredients, such as anti-oxidants, vitamins (A, C, ascorbic acid, B's, such as B1, thiamine, B6, pyridoxine, B complex, biotin, choline, nicotinic acid, pantothenic acid, B12, cyanocobalamin, and/or B2, D, D2, D3, calciferol, E, such as tocopherol, riboflavin, K, K1, K2). Preferred compounds, include, e.g creatine monohydrate, pyruvate, L-Carnitine, .alpha.-lipoic acid, Phytin or Phytic acid, Co Enzyme Q10, NADH, NAD, D-ribose, amino acids such as L-Glutamine, Lysine, chrysin; pre-hormones such as 4-drostenedione, 5-androstenedione, 4(or 5-)androstenediol, 19-nor-4 (or 5-)-drostenedione, 19-nor-4 (or 5-)-androstenediol, Beta-ecdysterone, and 5-Methyl-7-Methoxy Isoflavone. Preferred active ingredients include, e.g., pine pollen, fructus lycii, hippophae rhamnoides, Salvia Miltiorrhiza, Ligusticum, Acanthopanax, Astragalus, Ephedra, codonopsis, polygola tenuifolia Willd, Lilium, Sparganium, ginseng, panax notogiseng, Garcinia, Guggle, Grape Seed Extract or powder, and/or Ginkgo Biloba.

Brief Summary Text (13):
Other active agents include, e.g., antioxidants, anti-carcinogens, anti-inflammatory agents, hormones and hormone antagonists, antibiotics (e.g., amoxicillin) and other bacterial agents, and other medically useful drugs such as those identified in, e.g., Remington's Pharmaceutical Sciences, Eighteenth Edition, Mack Publishing Company, 1990. A preferred composition of the present invention comprises, about 1%-100%, preferably about 20-70% Rhodiola crenulata extract, more preferably about 60%, said extract having about 0.5-10% salidroside content; 10-45% 5:1 extracted fructus lycii powder (5 kilograms of the herb is used to produce 1 kg of herb powder); 1-20% of hippophae rhamnoides powder; and, optionally, a pharmaceutically-acceptable excipient.

Brief Summary Text (14):
The present invention relates to methods of administering Rhodiola, especially Rhodiola crenulata, e.g., to enhance blood oxygen levels, to enhance working capacity and endurance, to reduce muscle fatigue, to enhance memory and concentration, to reduce stress, to enhance cardiac and cardiovascular function, to improve sexual ability, to provide antioxidant effects, to protect against oxidation, to provide anti-cancer effects, to promote DNA repair, to provide anti-radiation effects, to protect against radiation, to reduce inflammation, to increase insulin, to decrease levels of glucagon, to reduce histamine release, to reduce allergic reactions, preferably, to modulate testosterone levels, to increase male virality, to modulate sleep, especially to promote sleep. to modulate blood lipids, preferably, e.g., to lower cholesterol levels, to promote weight loss, to increase estradiol levels, etc., and other conditions and diseases as mentioned above and below.

Brief Summary Text (20):
Any effective amount of Rhodiola crenulata can be administered. In accordance with present invention, it has been demonstrated that intake of a standardized Rhodiola crenulata extract (e.g., having 0.1-10%. Preferably 1-6%) salidroside by total weight of composition) produced a significant increase in total testosterone as compared to placebo. For example, after taking 2 grams of standardized rhodiola extract with 2% salidroside, once a day for a month, subjects showed about a 76% increase in total testosterone in the blood as compared to the 6.0% increase in total testosterone level after taking placebo for a month. These amounts, however, can be increased by any value, e.g., at least about 5%, 10%, 15%, 20%, 50%, 60% 70%, 75%, 100%, 2-fold, 5-fold, etc., over amounts which are present in the blood prior to administration.

Brief Summary Text (30):

Rhodiola can also be used to enhance or improved memory and concentration (such improved functions are to be distinguished from the more general brain stimulation which indicates increased non-selective neuronal activity, whereas the mentioned improved functions are selective, e.g., by stimulating specific parts of the brain or other organs, or by stimulating specific neural and hormonal systems); to reduce stress, e.g., lower blood pressure, reduce anxiety, promote calmness; to enhance cardiac and cardiovascular function (including, e.g., to protect against heart disease); to provide antioxidant effects and protect against oxidation; to provide anti-cancer effects, e.g., promote cessation of cell growth; to promote DNA repair; to provide anti-radiation effects and to protect against radiation, e.g., as a sun-screen when applied topically to the skin; to reduce inflammation, e.g., systemic inflammation, skin inflammation (where Rhodiola can be administered topically), but with the proviso that it is not lung-inflammation, coughing, or bleeding associated with lung-inflammation and coughing, to increase insulin, to decrease levels of glucagon, to reduce histamine release, to reduce allergic reactions, to enhance sexual ability. Rhodiola crenulata in accordance with the present invention is preferably not used to treat external wounds, external burns, lung inflammation, and coughing.

Detailed Description Text (29):
A composition comprising effective amounts of Rhodiola crenulata can be administered to subjects to enhance levels of blood oxygen, to enhance working capacity and endurance, to enhance memory and concentration, to reduce stress, to enhance cardiac and cardiovascular function, to provide antioxidant effects, to modulate testosterone levels, to modulate sleep, and to improve sexual performance. to increase energy level, and to enhance memory and concentration. Such a composition can comprise, by weight:

☐ 6. Document ID: US 20020119933 A1 WO 200209727 A1 AU 200178197 A US 6429198 B1

L5: Entry 6 of 6 File: DWPI Aug 29, 2002

DERWENT-ACC-NO: 2002-227074
DERWENT-WEEK: 200259

TITLE: Composition useful for improving cardiovascular function comprises D-ribose in combination with a vasodilator

Basic Abstract Text (1):
NOVELTY - A composition comprises D-ribose (I) in combination with a vasodilator (II).

Basic Abstract Text (5):
ADVANTAGE - The composition provides improvement of physical capability and enhancement of quality of life of the patient.

Equivalent Abstract Text (1):
NOVELTY - A composition comprises D-ribose (I) in combination with a vasodilator (II).

Equivalent Abstract Text (5):
ADVANTAGE - The composition provides improvement of physical capability and enhancement of quality of life of the patient.

Equivalent Abstract Text (6):
NOVELTY - A composition comprises D-ribose (I) in combination with a vasodilator (II).

Equivalent Abstract Text (10):
ADVANTAGE - The composition provides improvement of physical capability and enhancement of quality of life of the patient.

Standard Title Terms (1):
COMPOSITION USEFUL IMPROVE CARDIOVASCULAR FUNCTION COMPRISE RIBOSE COMBINATION VASODILATING

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Term	Documents
CARDIOVASCULAR.DWPI,TDBD,EPAB,JPAB,USPT,PGPB.	41227
FUNCTION.DWPI,TDBD,EPAB,JPAB,USPT,PGPB.	1841461
(4 AND (CARDIOVASCULAR ADJ FUNCTION)).USPT,PGPB,JPAB,EPAB,DWPI,TDBD.	6
(L4 AND CARDIOVASCULAR FUNCTION).USPT,PGPB,JPAB,EPAB,DWPI,TDBD.	6

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